ALLOPURINOL AND RISK OF BENIGN PROSTATIC HYPERPLASIA IN A FINNISH POPULATION-BASED COHORT

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Hyperurikemiaan liittyvän oksidatiivisen stressin on esitetty edistävän prostatan hyvänlaatuista liikakasvua (BPH). Ei tiedetä, olisiko antihyperurikemisella lääkityksellä vaikutusta BPH riskiin. Tutkimme BPH:n ja antihyperurikemisen allopurinolin käytön yhteyttä.

Kohortin muodostavat 74,745 miestä, jotka on alun perin identifioitu suomalaiseen eturauhassyövän seulontatutkimukseen (FinRSPC). Suljimme pois miehet, joilla oli BPH seurannan alussa. Käytimme Cox:n regressiomallia verrataksemme BPH lääkityksen, diagnoosin tai leikkauksen riskiä allopurinolin käytön mukaan. Lääkekäyttöä analysoitiin aikariippuvaisena muuttujana minimoidaksemme kuolemattomuusharhan vaikutusta.

Allopurinolin käyttäjillä oli ei-käyttäjiä pienempi riski kaikille BPH päätetapahtumille: monivakioidussa analyysissä BPH lääkityksen (HR 0.81; 95% CI 0.75-0.88), kirjatun BPH diagnoosin (HR 0.78; 95% CI 0.71-0.86) ja BPH leikkauksen (HR 0.67; 95% CI 0.58-0.76) riskit olivat alhaisemmat ei-käyttäjiin verrattuna. Painoindeksi (BMI) muokkasi riskisuhdetta; allopurinolin käyttö oli yhteydessä madaltuneeseen BPH riskiin vain miehillä, joiden painoindeksi oli tutkimusväestön mediaanin (27,3 kg/m^2) yläpuolella; interaktioiden p-arvo < 0.05 kaikille päätetapahtumille.

Mahdollinen selitys voisi olla antihyperurikemisen allopurinolin antioksidatiivinen vaikutus tai ksantiinioksidaasientsyymin toiminnan esto.

Tämän opinnäytteen alkuperäisyys on tarkastettu Turnitin OriginalityChek-ohjelmalla Tampereen yliopiston laatujärjestelmän mukaisesti.

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1 ABSTRACT

1.1 Background

Metabolic syndrome and obesity are linked with hyperuricemia, and it has also been proposed that oxidative stress associated with hyperuricemia may promote benign prostatic hyperplasia (BPH). However, it is currently unknown whether use of antihyperuricemic medication is associated with risk of developing BPH. We studied the association between BPH and use of antihyperuricemic allopurinol in a Finnish population-based cohort.

1.2 Methods

The study cohort consisted of 74,754 men originally identified for *the Finnish Randomized Study of Screening for Prostate Cancer (FinRSPC).* Information on gout and BPH medication usage (5α-reductase inhibitors, 5ARIs) during 1996-2014 was obtained from the national medication reimbursement database. Information on BPH diagnoses from in- and outpatient hospital visits and BPH-related surgery was obtained from the National Health Care Registry. Men with a record of BPH at baseline were excluded. We used Cox regression to analyze risk of starting BPH medication, having a recorded diagnosis or undergoing BPH surgery by allopurinol use with adjustment for age and simultaneous use of statins, antidiabetic or antihypertensive drugs and aspirin or other NSAIDs. Medication use was analyzed as a time-dependent variable to minimize immortal time bias.

1.3 Results

Men using allopurinol had a decreased risk for all three BPH endpoints: BPH medication (HR 0.81; 95% CI 0.75-0.88), BPH diagnosis (HR 0.78; 95% CI 0.71-0.86) and BPH-related surgery (HR 0.67; 95% CI 0.58-0.76) after multivariable adjustment. The risk association did not change by cumulative use. The risk decrease disappeared after one to two years lag time. Only BMI modified the risk association; the risk decrease was observed only among men with BMI above the median (27.3 kg/m^2); p for interaction < 0.05 for each endpoint.

1.4 Conclusions

We found that allopurinol use is associated with lowered risk of BPH medication, diagnosis and surgery. A possible explanation could be antioxidative effects of urate-lowering allopurinol.

2 INTRODUCTION

Benign Prostatic Hyperplasia (BPH) is a common problem among elderly men, but the etiology is partly unclear. Age is an established risk factor, but knowledge on modifiable risk factors is limited. Some studies have suggested that metabolic syndrome (MBS) and related hyperinsulinemia may together increase the risk of BPH – but results are inconsistent (1). Also type II diabetes and treated hypertension might be risk factors for BPH. (2)

Gout and hyperuricemia have been reported to associate with chronic inflammation and with oxidative stress, and there is some evidence that these factors are connected to prostate cancer and possibly also to BPH. (3,4) Oxidative stress has been suggested to be of importance in BPH pathogenesis. (5) *In vitro* uric acid accelerates prostate cancer cell growth. (6) In epidemiological studies prostate cancer and BPH seem to share risk factors. (7) Gout patients have been reported to have increased risk of urological cancers. (8) In rats allopurinol reduces oxidative stress in the prostate (9). Thus, in theory, allopurinol could reduce risk of BPH by reducing oxidative stress associated with obesity and hyperuricemia.

Xanthine oxidase is the main enzyme for uric acid formation and it can also oxidize nicotinamide adenine dinucleotide (NADH), which induces formation of reactive oxygen species (ROS). (10) Allopurinol Inhibits xanthine oxidase, thus lowering oxidative stress. (11) Allopurinol is the main antihyperuricemic drug in clinical use, although before 2014 also probenecid was used in Finland for the same indication. Mechanism of action differs between the two drugs, probenecid increases uric acid clearance (12).

Gout is associated with obesity, which is also associated with an increased BPH risk (13). However, it is unknown whether a direct association exists between gout and BPH. The role of hyperuricemia in the risk association between obesity and BPH has not been established. Furthermore, it is not known whether us of antihyperuricemic drugs, such as antioxidative allopurinol might affect the risk or severity of BPH.

We evaluated the association of antihyperuricemic medication usage and BPH in a population-based cohort study.

3 MATERIALS AND METHODS

3.1 Study cohort

Our study cohort comprises of men 55-67 years old at baseline, originally identified for the Finnish Randomized Study of Screening for Prostate Cancer (FinRSPC) in 1996-1999. (14) In total 80,458 men living in metropolitan areas of Helsinki and Tampere were identified from Population Register Centre and randomized either to undergo PSA screening at four year intervals or to be followed up through national registries. Prevalent prostate cancer cases at baseline were excluded.

The study cohort was linked to the national health care registry (HILMO) maintained by the National Institute for Health and Welfare. HILMO records all diagnoses and procedures during in- and outpatient hospital visits at Finnish health care units. Diagnoses made in the primary health care are not recorded.

All men with a recorded BPH diagnosis from in- and outpatient hospital visits (ICD-10 Code N40), BPH surgery (KED00, KED10, KED22, KED33, KED52, KED62, KED72 and KED76) or BPH medication (5α-reductase inhibitors, 5ARIs) purchases registered before the screening trial baseline at 1996-1999 were excluded, leaving a cohort of 74,754 men without clinical BPH interventions at baseline.

Men in the FinRSPC screening arm were mailed a questionnaire in 2004-2008, which included questions on height and weight (15). These were used to calculate BMI. The information was available for 11,220 men.

3.2 Information on antihyperuricemic medication use

Information on antihyperuricemic drug purchases during years 1995-2014 were obtained from national prescription database maintained by the Social Insurance Institution of Finland, SII.
As a part of national health insurance SII reimburses 50-100% of the price of physician-prescribed drug purchases depending on the indication and severity of the condition indicating the drug use. The reimbursement is most often received as a price compensation at pharmacy. All Finnish citizens are entitled for the compensation. Each reimbursed drug purchase is recorded by the prescription database. Antihyperuricemic drugs are available in Finland only through a physician's

prescription, thus comprehensively recorded by the prescription database. The register does not record medications used during hospital inpatient periods or over-the-counter drugs.

Information from the prescription database includes the date, dose, package size, and number of packages for each purchase. The linkage to study cohort was carried out using personal identification number. Information on purchases of antihyperuricemic, BPH, antidiabetic, antihypertensive and cholesterol-lowering drugs as well as physician-prescribed purchases of NSAIDs and aspirin were extracted from the registry. Drug identification was based on drug-specific ATC codes.

For each calendar year, we calculated cumulative yearly total amount (doses), duration (number or years with recorded medication purchases regardless of the amount) and intensity (average number of doses per year of usage) of antihyperuricemic medication use. The yearly number of doses was calculated by dividing the yearly mg amount of a given drug with the drug-specific Defined Daily Dose (DDD) as listed by the WHO. (16)

3.3 Statistical analyses

Cox proportional hazards regression was used to estimate hazard ratios (HRs) and 95% confidence intervals (95% CI) separately for BPH medication use, BPH diagnosis and BPH surgery. The follow-up started at the FinRSPC baseline in 1996-1999 and continued until death, emigration, end of 2014 or first occurrence of the BPH endpoints. Time-metric was years and months since the FinRSPC baseline.

We use two different model adjustments to estimate BPH risk: age-adjusted and multivariable-adjusted model with further adjustment for use of statins, antidiabetic drugs, antihypertensive drugs, NSAIDs and aspirin.

Antihyperuricemic medication use was analyzed as time-dependent variable; user status, cumulative amount and duration of use and average yearly dose were updated prospectively for each follow-up year based on yearly recorded medication purchases.

Long term effects of medication use were evaluated in lag time analyses, where medication usage was lagged forward in the follow-up time and analyzed 1 to 3 years later than purchased independent of later usage. For example, medication purchases in 2002 were analyzed at 2005 in 3-

year lag time analysis. As information on gout medication use was available since 1995, usage before that time was assumed to be at the same level as in 1995.

In subgroup analyses possible risk modification by the background variables was estimated by stratifying the study population and testing statistical significance of interaction terms between the tested background variable and BPH risk. Effect modification was tested for BMI and NSAID use, as both are associated with gout and prostate cancer (17,18), possibly also with BPH.

Statistical significance of the observed differences in background characteristics were compared between users and non-users of antihyperuricemic drugs using Chi-square statistics (categorical variables) and Mann-Whitney U-test (continuous variables). All reported p-values are two-sided.

4 RESULTS

4.1 Population characteristics

A total of 9,015 men (12.1% of the cohort) had any antihyperuricemic medication use. Median follow-up time for any endpoint did not differ by antihyperuricemic medication use. Overall, the incidence if BPH endpoints was comparable between the users and non-users. Men using antihyperuricemic medication were also more often using other drugs: antihypertensive drugs (87.9% vs 63.9% among the users and non-users, respectively; $p<0.05$), antidiabetic drugs (32.4% vs 18.4%; $p<0.05$), cholesterol-lowering drug (57.2% vs 39.8%; $p<0.05$), NSAIDs (91.6% vs 76.9%; $p<0.05$) and aspirin (19.9% vs 15.0%; $p<0.05$). (TABLE 1)

4.2 Risk of BPH by antihyperuricemic drug use

Antihyperuricemic medication use was associated with decreased risk of starting BPH medication (age-adjusted HR 0.90; 95% CI 0.83-0.97, multivariable-adjusted HR 0.81; 95% CI 0.75-0.88). Also risk of BPH diagnosis was lower in antihyperuricemic drug users: (HR 0.85; 95% CI 0.77-0.93) age adjusted and (HR 0.78; 95% CI 0.71-0.86) multivariable adjusted. Strongest risk decrease was observed for BPH surgery; (HR 0.72; 95% CI 0.63-0.83) age adjusted and (HR 0.67 95% CI 0.58-0.76) multivariable adjusted. (TABLE 2)
No clear risk trends were observed by cumulative amount, years or intensity of antihyperuricemic drugs use for any BPH endpoint, although the risk estimates were protective in all strata of cumulative use (TABLE 2).

4.3 Long-term risk association between antihyperuricemic drugs and BPH

In lag time analyses the decreased risk for all BPH endpoints disappeared within two years after antihyperuricemic drug usage. The decreased risk of BPH diagnosis attenuated already one year after the usage. (TABLE 3).

4.4 Subgroup analyses

NSAID use did not modify the risk association between antihyperuricemic medication use and risk of BPH medication, BPH diagnosis, or BPH surgery. BMI did modify the risk association; only among men with BMI above the median (27.3kg/m^2) users of antihyperuricemic drugs had lowered

risk of all BPH endpoints (p for interaction 0.008 (medication), 0.025 (diagnosis), and 0.001 (surgery)) (TABLE 4).

4.5 Sensitivity analyses

During the study period only two gout drugs were in use, allopurinol and probenecid. Antihyperuricemic drug use observed in our study consisted almost entirely of allopurinol use, as there were only 67 men using probenecid. Analysis limited to probenecid users only showed no risk difference for BPH between the users and non-users (Supplementary table). Therefore, the observed risk decrease by antihyperuricemic drug use are due to allopurinol.

5 DISCUSSION

Despite gout and BPH occurring in the same age group, to our knowledge, this is the first study to estimate the risk association between the use of allopurinol and BPH. Risk for BPH was found to be lower in men who use allopurinol compared to non-users. The finding is unexpected, as men with gout often have risk factors for BPH, such as obesity. One explanation for the association could be that the most commonly used antihyperuricemic drug, allopurinol, has also antioxidant effects (19). The risk decrease was stronger in men with BMI above the median (27.3kg/m^2), i.e. among men with presumably higher risk for BPH. Thus allopurinol may lower the increased risk of BPH among overweight men by decreasing oxidative stress and chronic inflammation related to obesity (20). To our knowledge, possible beneficial effects of allopurinol against prostatic disease has not been previously estimated in epidemiological studies. Our study supports the benefits of antihyperuricemic drug use as it was associated with decreased risk for all three BPH endpoints.

Allopurinol inhibits enzyme xanthine oxidoreductase, which catalyzes the last two reactions in the urea cycle: hypoxanthine moving to xanthine and further to uric acid. Uric acid has been associated with oxidative stress-related conditions, such as cardiovascular disease. (21) Oxidative stress is also a risk factor for BPH. (22) Thus inhibition of xanthine oxidase provides a possible biological mechanism for beneficial effects of allopurinol against BPH.

Another possible mechanism for benefits of allopurinol use is systemic lowering of uric acid level. Previous laboratory studies have suggested that elevated uric acid level may increase oxidative stress in the prostate, whereas allopurinol use may lower it. (6,9) Nevertheless, we did not have information on uric acid levels and therefore could not assess its role directly. It has to be considered, that the risk decrease could be caused by other background factors.

Possible confounding factor is that medication users, such as allopurinol user, may be more active users of health services, with more frequent physician contacts. This may lead to more frequent diagnoses of asymptomatic BPH. We could not adjust for this possible confounder as we did not have information on prostate volumes. However, this possible confounder would increase the risk estimates among allopurinol users, and thus does not limit our inference of decreased BPH risk.

Concordant to previous studies (13), BMI was an effect modifier; the inverse association between gout medication and BPH risk was strongest in men with BMI above the median. The finding could

be a consequence of the connection between obesity and oxidative stress. (23) The antioxidant effect of allopurinol may be stronger in men with higher level of oxidative stress due to obesity.

Our study has many strengths. Our large study cohort was population-based, collected from Finnish national registries and thus free of biases often associated with survey-based cohorts, such as recall bias. Large cohort size minimized the effect of random error. Also, information on three BPH endpoints from national health care registries was detailed and reliable. Information on antihyperuricemic medication use from the SII prescription database allowed us to evaluate medication use on a year-by-year basis. Additionally, we had extensive information on use of other drugs often used together with antihyperuricemic drugs, such as NSAIDs. Thus, we were able to control for confounding by medication use for other indications.

Our study also has limitations. Prostate sizes were not available, and our data on BPH relied solely on indirect estimators BPH-related procedures, diagnoses and 5α-reductase inhibitor use recorded by the registries. Prevalence of subclinical BPH is high in this age-group, and missing information on actual prostate sizes allowed selection bias of more subclinical BPH being detected among men contacting a physician due to gout symptoms. Only limited information on BMI was available, and we did not have information on lifestyle factors such as diet, smoking and physical activity, which could have caused confounding. We aimed to minimize confounding by comorbidities such as diabetes by using model adjustments, but residual confounding is always possible.

In conclusion, we observed that use of antihyperuricemic medication was associated with lowered risk of starting BPH medication, having BPH diagnosis and undergoing BPH surgery, especially in overweight men. The finding supports previous reports of beneficial effects of allopurinol in the prostate. If confirmed in further studies, allopurinol may prove to be beneficial against development of clinically significant BPH.

6 CONFLICT OF INTERESTS

TLJ Tammela: consultant fees from Astellas, Bayer and Roche

TJ Murtola: consultant fees from Astellasand Janssen Cilag. Lecture fees from Astellas, GSK and Janssen Cilag.

K Taari: Consultant fee from Abbvie, research funding from Medivation, travel support from Astellas, and Orion

Other authors declare no conflict of interests.

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8 TABLES

8.1 Table 1

Population characteristics by antihyperuricemic drug use. Study cohort of 74 754 men free of BPH at baseline.

	Antihyperuricemic medication	
	Non-users	Users
N of men	65 739	9 015
N (%) of BPH medication**	13 115 (20.0%)	1 841 (20.4%)
N (%) of BPH diagnoses**	8 867 (13.5%)	1 229 (13.6%)
N (%) of men undergoing BPH surgery	5 079 (7.7%)	648 (7.2%)
Median (IQR) follow-up until BPH medication	16.0 (10.6-18.0)	16.0 (10.9-17.6)
Median (IQR) follow-up until BPH dg	16.0 (12.6-18.0)	16.0 (12.6-18.0)
Median (IQR) follow-up until BPH surgery	16.2 (13.3-18.0)	16.0 (13.2-18.0)
Median (IQR) age at baseline	59 (55-63)	59 (55-63)
Median (IQR) BMI	26.1 (24.2-28.7)	28.1 (25.8-31.0)*
Antihypertensive drug users; n (%)	42 011 (63.9%)	7 922 (87.9%)*
Antidiabetic drug users; n (%)	12 105 (18.4%)	2 920 (32.4%)*
Cholesterol-lowering drug users; n (%)	26 167 (39.8%)	5153 (57.2%)*
NSAID users; n (%)	50 555 (76.9%)	8 262 (91.6%)*
Aspirin users; n (%)	9 845 (15.0%)	1 794 (19.9%)*

* $P < 0.05$ for difference in observed differences compared to non-users. Calculated with Mann-Whitney U-test for continuous variables (BMI), chi-square test for categorical variables.
** BPH diagnoses recorded from secondary health care only, medication use includes also prescriptions from primary health care. BPH medication use defined as recorded purchases of either finasteride or dutasteride.

8.2 Table 2

Risk of BPH by antihyperuricemic drug use. Study cohort of 74 754 men free of BPH at baseline.

		Risk of BPH medication		Risk of having recorded BPH diagnosis		Risk of BPH surgery	
	N	**HR (95% CI)** Age adjusted	**HR (95% CI)** Multivar.adjusted	**HR (95% CI)** Age adjusted	**HR (95% CI)** Multivar.adjusted	**HR (95% CI)** Age adjusted	**HR (95% CI)** Multivar.adjusted
Gout drug use							
Non-user	65 739	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Any user	9 015	0.90 (0.83-0.97)	0.81 (0.75-0.88)	0.85 (0.77-0.93)	0.78 (0.71-0.86)	0.72 (0.63-0.83)	0.67 (0.58-0.76)
Cumulative amount							
Tertile1 (DDD <125.00)	3 143	0.88 (0.73-1.05)	0.82 (0.68-0.98)	0.83 (0.66-1.04)	0.78 (0.62-0.98)	0.75 (0.54-1.03)	0.71 (0.51-0.98)
Tertile2 (DDD =125.00-600.00	2 924	0.84 (0.74-0.97)	0.77 (0.67-0.88)	0.87 (0.74-1.03)	0.81 (0.68-0.95)	0.80 (0.64-1.01)	0.74 (0.59-0.93)
Tertile3 (DDD >600.00)	2 948	0.94 (0.84-1.05)	0.85 (0.76-0.95)	0.84 (0.74-0.96)	0.77 (0.67-0.88)	0.67 (0.55-0.81)	0.61 (0.50-0.74)
Cumulative years of use							
tertile1 (years <2)	3 755	0.85 (0.73-0.99)	0.79 (0.67-0.92)	0.80 (0.66-0.98)	0.75 (0.62-0.92)	0.75 (0.57-0.99)	0.71 (0.53-0.94)
Tertile2 (years 2-6)	2 681	0.94 (0.82-1.07)	0.85 (0.74-0.97)	0.86 (0.72-1.01)	0.79 (0.67-0.94)	0.80 (0.64-1.01)	0.74 (0.59-0.93)
Tertile3 (years >6)	2 579	0.89 (0.79-1.01)	0.80 (0.71-0.91)	0.86 (0.75-0.99)	0.79 (0.69-0.91)	0.66 (0.54-0.81)	0.60 (0.49-0.74)
Average intensity of use							
Tertile1 (Intensity <62.50)	3 102	0.85 (0.72-1.02)	0.79 (0.67-0.94)	0.89 (0.73-1.08)	0.83 (0.68-1.01)	0.71 (0.53-0.96)	0.67 (0.50-0.90)
Tertile2 (Intensity 62.00-112.50)	3 001	0.85 (0.74-0.98)	0.77 (0.67-0.89)	0.84 (0.71-0.98)	0.77 (0.66-0.91)	0.84 (0.67-1.03)	0.77 (0.62-0.96)
Tertile3 (Intensity >112.50)	2 912	0.95 (0.85-1.06)	0.85 (0.76-0.96)	0.84 (0.73-0.96)	0.77 (0.67-0.89)	0.64 (0.52-0.80)	0.59 (0.47-0.72)

8.3 Table 3

Long-term association between antihyperuricemic drug use and BPH risk. Study cohort of 74 754 men free of BPH at baseline.

	Main analysis HR (95 CI) multivar adjusted	**1v lag time** multivar adjusted	**2v lag time** multivar adjusted	**3v lag time** multivar adjusted
BPH medication	0.81 (0.75-0.88)	0.87 (0.81-0.95)	0.93 (0.86-1.00)	0.92 (0.85-1.00)
BPH diagnosis	0.78 (0.71-0.86)	0.93 (0.85-1.02)	0.98 (0.90-1.07)	0.96 (0.87-1.05)
BPH surgery	0.67 (0.58-0.76)	0.85 (0.75-0.96)	0.88 (0.78-1.00)	0.90 (0.79-1.01)

8.4 Table 4

Risk of BPH by antihyperuricemic drug use in subgroup analysis stratified by NSAID use and BMI. Study cohort of 74 754 men free of BPH at baseline.

	BPH medication HR (95% CI) age adjusted	**BPH diagnosis HR (95% CI)** age adjusted	**BPH surgery HR (95% CI)** age adjusted
NSAID user	0.84 (0.78-0.91)	0.81 (0.74-0.89)	0.68 (0.59-0.79)
NSAID non user	0.90 (0.61-1.31)	0.81 (0.51-1.27)	0.98 (0.57-1.69)
P for interaction	0.712	0.382	0.971
BMI > median (27.3kg/m^2)	0.68 (0.54-0.86)	0.49 (0.36-0.69)	0.55 (0.35-0.87)
BMI < median (27.3kg/m^2)	0.96 (0.68-1.36)	0.90 (0.59-1.37)	1.06 (0.62-1.80)
P for interaction	0.008	0.025	0.001

8.5 Supplementary table

Risk of benign prostatic hyperplasia (BPH) among probenecid users compared to non-users. Study cohort of 74 754 men free of BPH at baseline.

		Risk of BPH medication use	**Risk of having recorded BPH diagnosis**	**Risk of BPH surgery**
	N	**HR (95% CI)** **Multivar.adjusted**	**HR (95% CI)** **Multivar.adjusted**	**HR (95% CI)** **Multivar.adjusted**
Probenecid use				
Non-user	74 687	Ref.	Ref.	Ref.
Any user	67	1.17 (0.38-3.64)	1.03 (0.14-7.28)	1.86 (0.26-13.24)